For the reasons given below, Applicants respectfully submit that the amended and newly presented claims are in condition for allowance, and notification to that effect is earnestly solicited.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 15-16 under 35 U.S.C. § 112, first paragraph. The Examiner asserted that the claims should be limited to *in vitro* methods.

Without acquiescing to the Examiner's rejection or reasoning, and solely to advance prosecution of the present application, Applicants have amended claim 15 to recite an *in vitro* method. Similarly, newly presented claim 22 recites an *in vitro* method.

Thus, this rejection is rendered moot.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-14 and 17-18 under 35 U.S.C. § 103(a) as obvious over *Choli et al.* (Antisense Res. and Dev. 4:19-26, 1994), *Naldini et al.* (Science 272:263-267, 1996), *Hope et al.* (PNAS, 87:7787-7791, 1990) and *Lisziewicz* (WO92/21750, 1992). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the cited documents, *Choli et al.* (1994), *Naldini et al.* (1996), *Hope et al.* (1990) and *Lisziewicz* (WO 92/21750) either alone or in combination do not disclose or suggest the retroviral vectors of the present invention.

Choli et al.

In this respect, the disclosure in *Choli et al.* relates *inter alia* to the inhibition of Rev-RRE interaction in order to block the HIV-1 life cycle before viral structural proteins are produced. Accordingly, *Choli et al.* (1994) disclose retroviral vectors expressing chimeric RNAs containing HIV-1 RRE and HIV-1 packaging signal in sense and antisense orientations.

Choli et al (1994) do not disclose or suggest:

(i) a retroviral vector whereby the selected gene is contained within an intron or;

(ii) if a selected gene is located within an intron, the Rev/RRE system may be used to manipulate the expression of the therapeutic gene.

Consequently, on reading *Choli et al.*, a skilled person would not have been motivated to prepare a retroviral vector, especially if a non-HIV vector is set out in the present invention. That is, the *Choli et al.* reference, either alone or in combination, neither teaches nor suggests the presently claimed invention.

Naldini et al.

Naldini et al. (1996) use a fragment of an HIV genome encompassing the normal major splice donor sequence, RRE and the normal splice acceptor sequence in the normal configuration in their transducing vector pHR'. RRE is therefore contained within the HIV env intron. This fragment is presumed and is likely, but not proven, to render the expression of the genome responsive to Rev.

In the vector described in *Naldini et al.* (1996), the coding sequence for the reporter gene lies outside of the RRE containing intron (see Figure 1) and the Rev/RRE system is not used to manipulate the expression of the therapeutic gene.

Therefore, the *Naldini et al.* (1996) reference, either alone or in combination, neither teaches nor suggests the presently claimed invention.

Hope et al.

Hope et al. use a reporter plasmid (pDM128) derived from the env region of HIV-1 (Fig. 1A) to show that cells transfected with the pDM128 plasmid alone yield only trace levels of CAT enzyme activity as a single intron containing a CAT coding sequence is excised when the RNA is spliced. However, co-transfection of cells with a functional Rev expression vector (pRSV-Rev) permit the unspliced transcripts to enter the cytoplasm, increasing CAT activity 75- to 100-fold thus implying the need for a functional protein.

Hope et al. does not disclose or suggest:

(i) an HIV retroviral vector or fragment thereof encompassing the normal major splice donor sequence, RRE an the normal splice acceptor sequence in the normal configuration in a HIV vector (as disclosed in Naldini et al. 1996);

(ii) any retroviral vector comprising a splice donor sequence, RRE and a splice acceptor sequence;

(iii) a retroviral vector with a selected therapeutic/reporter gene is contained within an intron; or

(iv) if a selected gene is located within an intron, the Rev/RRE system may be used to manipulate the expression of the therapeutic gene.

Consequently, on reading *Hope et al.*, a skilled person would not have been motivated to prepare a retroviral vector as set out in the present invention. That is, the *Hope et al.* reference, either alone or in combination, neither teaches nor suggests the presently claimed invention.

Lisziewicz

Lisziewicz (WO 92/21750) describe a non-lentiviral vector incorporating the Rev/RRE system whereby the RRE element is inserted into a retroviral vector or into an intron of a foreign gene contained within that vector. In contradistinction, the therapeutic gene of the present invention is located within an intron and the RRE is located within an intron but the RRE is not located within the intron of a therapeutic gene.

In addition, the constructions outlined in Lisziewicz make no reference to the presence of the splice donor sequence within the MLV vector, nor take into account any requirement for inefficient splicing to achieve Rev function, and there is no description of precisely where to insert the RRE. The disclosure therefore suggests that in constructing a retroviral vector whose expression is dependent upon Rev the nature and location of the RRE is not material and the nature and location of additional introns or splice sequences in not material.

Therefore, Applicants respectfully submit that *Choli et al.* (1994), *Naldini et al.* (1996), *Hope et al.* (1990) and *Lisziewicz* (WO 92/21750) do not teach or suggest the present invention and request withdrawal of this rejection.

CONCLUSION

In view of the amendments and remarks made herein, it is respectfully submitted that the application is in condition for allowance. Notification to that effect is earnestly requested.

Respectfully submitted,

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MARKED-UP VERSION TO SHOW CHANGES

~~Please~~ cancel claim 11 without prejudice.

Please amend claim 15 as follows.

15. (TWICE AMENDED) A method for inserting a selected gene into a target cell, the method comprising: contacting the target cell *in vitro* with the retroviral vector according to claim 1.

Claims 19-23 are new.